New Regulators of Spermatogonial Stem Cells: RHOX Homeobox Transcription Factors

Grant Award Details

New Regulators of Spermatogonial Stem Cells: RHOX Homeobox Transcription Factors

Grant Type: Basic Biology V

Grant Number: RB5-07210

Project Objective: This proposal tests the hypothesis that the transcription factor RHOX10 is required for mouse spermatogonial stem cell (SSC) self-renewal and that human RHOX transcription factors play roles in SSC biology. The findings may have implications for some forms of male infertility.

Investigator:

Name:	Miles Wilkinson
Institution:	University of California, San Diego
Type:	PI

Human Stem Cell Use: Adult Stem Cell

Award Value: $552,811

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: New Regulators of Spermatogonial Stem Cells: RHOX Homeobox Transcription Factors

Public Abstract:

Infertility afflicts a remarkably high percentage (~15%) of couples, with male factor defects being responsible for more than ½ of these cases. One-third of these male infertility cases have no known cause. For most infertile men, the only "treatment" is in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), both of which are costly, invasive for the female, and yield low pregnancy rates and even lower live birth rates. There is also evidence that the offspring born of IVF and ICSI procedures are at greater risk for developing a variety of conditions, including diabetes, obesity, and chromosome and epigenetic aberrations. Thus, there is a great need for alternative approaches, many of which revolve around knowing more about the stem cells in the testis—the spermatogonial stem cells (SSCs)—as they are essential for giving rise to sperm. Towards this goal, we have identified a regulatory gene that we have considerable evidence promotes the self-renewal of SSCs. In this application, we propose to elucidate the precise biological functions and molecular targets of this regulatory gene in SSCs. To determine its role in humans, we will use molecular approaches to knock down its expression in SSCs derived from human testicular biopsy samples. By determining the underlying mechanisms by which human SSCs self-renew, this research has the potential to generate novel therapies for male infertility, including for cancer patients rendered infertile due to chemotherapy.

Statement of Benefit to California:

Fertility defects are extremely common in human males. At least 7% of men of reproductive age in the U.S. are either infertile or subfertile. This translates to over 1 million men in California suffering from major fertility deficiencies. In contrast to women, only a very limited number of men with primary infertility have a medically treatable condition. Rather than direct treatment, male infertility is typically dealt with by in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Both of these procedures are associated with several risks, including chromosomal and epigenetic abnormalities, and they yield low pregnancy rates and even lower live birth rates. They are typically not covered by insurance in California and are extremely costly —$15,000 to $20,000 for a single cycle—and most couples undergo more than one cycle. In total, it is estimated that more than $40,000,000 million a year is spent on these procedures in California alone. This application is focused on new approaches for treating male infertility that revolve around using spermatogonial stem cells (SSCs). In addition to providing potential cures for idiopathic male infertility (~32% of male infertility cases in California), SSCs provide a source of germ cells for engendering fertility to patients undergoing cancer chemotherapy treatment. By expanding SSCs cryopreserved before such patients undergo chemotherapy, their fertility can later be restored by transplantation.
